Successful treatment of pure red cell aplasia in systemic lupus erythematosus with cyclosporin A

F. Atzeni, P. Sarzi-Puttini, F. Capsoni*, L. Vulpio, M. Carrabba

Department of Rheumatology, L. Sacco University Hospital, Milan; *I.R.C.C.S. Ospedale Policlinico, Department of Internal Medicine, University of Milan, Italy.

Fabiola Atzeni, MD; Piercarlo Sarzi-Puttini, MD; Franco Capsoni, MD; Laura Vulpio, MD; Mario Carrabba, MD.

Please address correspondence to: Fabiola Atzeni, MD, Rheumatology Unit, L. Sacco University Hospital, Via G.B. Grassi 74, 20157 Milan, Italy.

E-mail: atzenifabiola@hotmail.com

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ABSTRACT

We report a patient with longstanding systemic lupus erythematosus (SLE) who developed pure red cell aplasia (PRCA). This condition is rare in connective tissue diseases and is reported in 32 previous cases of SLE in literature. Our patient recovered, apparently in response to treatment with high dosage of corticosteroids, but relapse occurred when the prednisone dosage was tapered down to 10 mg/day. The patient was successfully treated with cyclosporin A with no recurrence of the disease in the last 2 years.

Introduction

Pure red cell aplasia (PRCA) is characterized by suppression of erythropoiesis with little or no abnormality of leukocyte or platelet production (1, 2). A rare congenital form (Diamond-Blackfan syndrome) appears early in childhood (3).

The acquired form may be primary but the association with thymoma, hemolytic anaemia, infections, malnutrition, connective tissue diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), malignancy, acute renal failure and certain drugs have been also described (1). To our knowledge, PRCA has been reported in 32 patients with SLE in the literature (4-22, 24-28) (Table 1). In 1 case it occurred in a patient with drug-induced SLE, probably caused by procainamide therapy (4); in 2 cases it was associated with primary autoimmune hypothyroidism (5, 6); in 5 cases it was associated with enteropathy (7); in 3 cases it was associated with a thymoma (8-10); and in other cases it appeared to be a simple association with SLE (11-22, 25-30).

Several treatment methods have been applied to this disorder, including corticosteroids, immunosuppressive agents, high dose intravenous immunoglobulins, plasmapheresis and erythropoietin (25-30). In particular, corticosteroids are the recommended initial mode of treatment for acquired PRCA. We describe the case of a female affected by SLE with longstanding PRCA, refractory to corticosteroids, treated successfully with cyclosporin A and summarize the previous cases reported in the literature.

Case report

A 42-year-old female presented to our outpatient clinic in 1991 with fever, butterfly rash, photosensitivity and non-erosive oligoarthritis. Laboratory study results were as follows: antinuclear antibodies (ANA) by indirect immunofluorescence were positive in a titre of 1:640 with a homogeneous pattern; anti-DNAtest (Chritidia Luciliae method was positive in a titre 1:80); antibodies to Sm, RNP, SSA and SSB were negative.

A diagnosis of SLE was made and the patient was treated with hydroxychloroquine (200 mg/day) and low doses of prednisone (10 mg/day); she improved slowly and after 12 months could be considered in complete remission. She was placed on maintenance therapy with hydroxychloroquine (100 mg/day) and prednisone (2.5 mg/day). She was followed up for 6 years at regular intervals and, despite being positive for antinuclear and anti-DNA antibodies and recurrent arthralgias, she remained reasonably well and change in therapy was not necessary.

In March 1999 she was admitted to our hospital because of a severe anaemia and increasing fatigue. Clinical examination revealed a pale woman with a blood pressure of 120/70 mmHg, pulse 120 beats/min and axillary temperature of 37.1°C. No other symptoms that could be related to a clinical picture of SLE were observed. Laboratory evaluation showed haemoglobin 5.3 g/dl; reticulocyte count 0.1%; white blood cell count (WBC) 6000/mm³ with a normal differential count; platelet count 192,000/mm³; a Coombs’ test (direct and indirect) was negative and there was no hyperbilirubinemia or elevation of the serum lactate dehydrogenase concentration. Specific serological tests for Epstein-Barr virus, adenovirus, cytomegalovirus, and human parvovirus specific IgM were all negative.

No signs of malnutrition were present and serum vitamin B12 and erythrocyte folate levels were normal. ANA(1:160) with a homogeneous pattern and anti-
DNA test (1:40) were positive. Radiography of chest showed no thymoma. A bone marrow aspirate showed severe erythroid hypoplasia with normal myeloid and platelet precursors and normal iron stores, allowing us to make a diagnosis of PRCA. She received 3 Units of packed red cells; the dosage of prednisone was increased to 75 mg/day in divided doses. A reticulocytosis (3%) occurred after 3 weeks and her haemoglobin level gradually normalized. The prednisone dosage was tapered to 10 mg/day within 3 months without relapse of PRCA. She was followed at regular intervals and her reticulocyte count stayed within normal values. In January 2000 she was rehospitalized because of a relapse of PRCA. A bone marrow aspirate showed similar results as described in the previous hospitalization. She was treated with 4 units of packed red cells and the prednisone dosage was increased again to 75 mg/day but 8 weeks later when the prednisone dosage was tapered to 10 mg/day the laboratory values dropped again (haemoglobin 6.5 g/dl, reticulocyte 0.4%). She was again transfused and started on cyclosporin A at dose of 200 mg/day with a complete remission of PRCA. Six months later cyclosporin was stopped and she was taking 10 mg/day of prednisone and had a haemoglobin level of 12.3 g/dl and reticulocyte count of 2.8%. No recurrence of PRCA was observed during the next 2 years of follow-up.

**Discussion**

Our patient had mild SLE and subsequently developed PRCA. Her platelet count remained normal; she had a mild intermittent leukopenia which may have related to the disease itself. Bone marrow examination did not show any decrease in granulocyte precursors or megakaryocytes.

Three particular aetiological factors may be considered in our patient with PRCA: drug ingestion, subclinical infection or an immunological disturbance related to the connective tissue disease. Several drugs are known to cause PRCA, but antimalarials are not included in this list of drugs classically related to its development (1, 4). Furthermore, she had been taking hydroxychloroquine for 8 years before the development of her aplasia and the cessation of this treatment did not prevent the relapse few months later.

In the absence of any demonstrable causative infective agent or drug, PRCA was regarded as a manifestation of SLE. PRCA should be considered when any patient with rheumatoid arthritis, SLE or other connective tissue...
disease develops severe anaemia in the absence of blood loss or haemolysis (11-16). The combination of SLE and PRCA is rare but probably underdiagnosed. Kiel et al. (17) have stated that renal and central nervous system involvement does occur in those with concomitant SLE and PRCA, but Habib et al. (18) have found a trend for less proteinuria and hallucinations and a significant decrease in pleuritis in those with SLE and PRCA.

PRCA can be considered as an immunologically mediated disease (19-21). Several mechanisms have been implicated in the pathogenesis of PRCA, including the formation of antibodies to erythroblasts (19), to erythroid colony forming units or to erythropoietin (20), as well as the immune-mediated suppression of erythropoiesis (21). The exact nature of the target antigen on the erythroblast or the erythroid progenitor is not clear, but it has been suggested that the autoantibody may recognize and bind to the erythropoietin receptor (21). T-cell mediated inhibition of erythropoiesis may also be involved in the pathogenesis of the SLE associated PRCA, while its role in lymphoproliferative disorders associated PRCA is well established (19).

Corticosteroids have been effective in both congenital and acquired forms of PRCA (22). Nearly 50% of the patients respond to conventional dosages of prednisone 1-2 mg/Kg alone within 4 weeks. These rates increase when steroids are used in combination with other immunosuppressive drugs such as azathioprine, cyclophosphamide, and cyclosporin A (23). Cyclosporin A is an effective biological immunosuppressive agent; favourable results have been obtained with this treatment in acquired PRCA (24, 25). Other agents that have been used successfully include danazol, 6-mercaptopurine, antilymphocytic and antithymocytic globulin (23). The value of combined treatment with steroids and cytotoxic drugs has been demonstrated by a higher remission rate, but such vigorous immunosuppressive treatment increases the risks of serious infections, malignancy, sterility and other side effects.

Other less frequently used approaches for the management of SLE-associated PRCA are plasmapheresis, lymphapheresis, and high dose intravenous immunoglobulins (IVIG) (26). Plasmapheresis has been used as a therapeutic modality for PRCA; in fact, the removal by plasmapheresis of the multiple autoantibodies detected in SLE may result in complete remission of erythropoiesis (27, 28). Messner et al. suggest that a factor in the plasma substitute may provide or induce the release of erythropoietic stimulators with burst-promoting activity (29).

Recently some authors reported cases of refractory PRCA treated with recombinant human erythropoietin (EPO) with satisfactory results (30). The relatively low toxicity of erythropoietin, its lack of immunosuppressive and bone marrow depressant activity, makes this agent a rational therapeutic option in pure red aplasia in general and in SLE in particular (30). SLE-associated PRCA is a rare disorder whose optimal management has remained uncertain. We report a case of a patient with PRCA and SLE who failed to respond to corticosteroids but was then successfully treated with cyclosporin A with a persistent remission. Our experience and the literature suggest that cyclosporin A at a dose of 200 mg/day for a 6-month treatment period is a potential alternative in patients with PRCA and SLE refractory to corticosteroids; the treatment duration and the length of remission remain to be elucidated.

References